Please replace paragraph 1, beginning at line 10 of page 1 with the following replacement paragraph:

--This application is a continuation-in-part of 09/018,226, now U.S. Patent No. 6,150,416, issued November 21, 2000, and claims the benefit of that application, U.S. Provisional Application No. 60/125,958, filed March 24, 1999, and U.S. Provisional Application No. 60/036,903, filed February 4, 1997, the disclosures of which are incorporated by reference. This invention was made with Government support under Grant (Contract) Nos. RO1 GM53696 and RO1 GM50353 awarded by the National Institutes of Health. The Government has certain rights in this invention.--

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REMARKS

The specification has been amended to reflect the current status of U.S. Patent Application No. 09/018,226. No new matter has been added. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

1. Status of the Claims and Outstanding Rejections

Claims 1-50 are pending in the above-referenced patent application; claims 1-50 are currently under examination. In the Office Action, claims 1-50 have been rejected under 35 U.S.C. § 101. Claims 1-50 have also been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. Claims 1-35 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 36-50 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled because they relate to treating neurodegenerative disorders. In addition, claims containing "substituted alkyl",

"substituted aryl", and "substituted heteroaryl" have been rejected for allegedly lacking limitations to the possible substituents claimed. For the reasons set forth herein, each of the Examiner's rejections is overcome.

2. ***Amendment/Priority Claim***

The specification has been amended, as suggested by the Examiner, to include the current status of U.S. Patent Application No. 09/018,226, now U.S. Patent No. 6,150,416, issued November 21, 2000.

3. ***Rejection under 35 U.S.C. § 101***

Claims 1-50 have been rejected under 35 U.S.C. § 101 as allegedly lacking utility. The Examiner has rejected claims 1-50, stating that the claimed invention is not supported by either a credible utility or a well-established utility. In response, Applicants respectfully direct the Examiner's attention to the attached Declaration of Dr. Xiaoning Bi, pursuant to 37 C.F.R. § 1.132.

In this Declaration, Dr. Bi asserts that the present invention has a specific, substantial and credible utility in that claims 1-50 are directed to specific methods of use. According to Dr. Bi, the data set forth in the specification unequivocally establishes that the aspartyl protease inhibitors of Formula I of the present invention can be used to modulate the processing of an APP and/or a tau-protein (τ-protein). Furthermore, with regard to independent claim 36 and dependent claims 37-50, which are directed to a method for treating a neurodegenerative disorder, the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor of Formula I, Dr. Bi sets forth the following:

> [t]o my knowledge as one of skill in the art, neurodegenerative disorders that can be treated using the aspartyl protease inhibitors of the present invention include, for example, those neurodegenerative disorders characterized by the accumulation of amyloid plaques or τ-protein. It is well-known in the art that such plaques contain large amounts of Aβ. Clearly, therapeutic agents

> that can decrease the formation of Aβ, as do the aspartyl protease inhibitors of the present invention, can play a beneficial role in retarding the progression of these neurodegenerative disorders. Examples of such neurodegenerative diseases include, but are not limited to, the following: Alzheimer's disease, Parkinson's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia (*e.g.*, dementia pugilistica) and head trauma. As explained above and as demonstrated in the specification, the aspartyl protease inhibitors of Formula I of the present invention can be used to modulate the processing of an APP and a τ-protein. Thus, the claimed invention has a specific, substantial and credible utility in that claims 36-50 are directed to a method of use, and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use.

As explained by Dr. Bi, therapeutic agents that can decrease the formation of Aβ, as do the aspartyl protease inhibitors of the present invention, can play a beneficial role in retarding the progression of these neurodegenerative disorders. As stated above, claims 36-50 are directed to a method for treating a neurodegenerative disorder the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor of Formula I. Thus, according to Dr. Bi, the claimed invention has a specific, substantial and credible utility in that claims 36-50 are directed to a method of use, and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use.

The Office Action has cited Wagner and Munoz, "Modulation of amyloid β protein precursor processing as a means of retarding progression of Alzheimer's disease", *The Journal of Clinical Investigation*, (1999) 104(1):1329-1332 ("Wagner *et al.*"), in support of the rejection under 35 U.S.C. § 101. In the Declaration, Dr. Bi sets forth the following:

> [i]t is my opinion that Wagner *et al.*, in fact, strongly support the modulation of APP processing as a mode of AD therapy.
>
> According to Wagner *et al.*:

> [t]he pathogenetic findings, combined with a rather voluminous body of literature, implicate Aβ peptides in some neurotoxic and/or pathophysiological process and ***strongly suggest that therapeutic approaches aimed at modulating the proteolytic catabolism of APP or reducing $A\beta_{42}$ formation might provide fruitful clinical results***.

See, page 1329, second column, lines 31-37, Wagner *et al.*

Clearly, Wagner *et al.* strongly support of the use of APP processing modulators as therapeutic agents for treating Alzheimer's disease.

According to Dr. Bi, Wagner *et al.* clearly support the use of modulators of APP processing, such as the aspartyl protease inhibitors of Formula I of the present invention, in treatment of Alzheimer's disease. Furthermore, Dr. Bi explains that Wagner *et al.* clearly set forth that available transgenic mouse models are useful for assessing the *in vivo* efficacy of compounds that modulate Aβ levels in cultured cell systems, and that such compounds are expected to reach the clinic soon. Dr. Bi sets forth the following:

> [s]upports the use of the transgenic mouse models to validate the *in vivo* efficacy of the compounds described in Wagner *et al.* that are capable of eliminating Aβ levels in cultured cell systems.

According to Wagner *et al.*:

> [t]hese transgenic models could serve as extremely useful reagents for assessing the *in vivo* efficacy of compounds, such as those described previously, that are capable of eliminating, or at least diminishing Aβ levels in cultured cell systems. In fact, ***compounds that have been shown to reduce Aβ peptide levels in transgenic mice are expected to reach the clinic soon***...Although none of the currently available models recapitulate the entire scope of behavioral and pathological features of AD, ***they do provide excellent tools for examining***

> ***not only potential drugs, but also genetic and environmental modifiers of this dreaded disease.***
>
> *See*, page 1332, paragraph spanning columns 1 and 2, Wagner *et al.*

Thus, according to Dr. Bi and Wagner *et al.*, compounds that modulate APP processing, such as the aspartyl protease inhibitors of Formula I of the present invention, are useful for treating neurodegenerative disorders characterized by the presence of neuritic plaques containing large amounts of Aβ peptide. In fact, Wagner *et al.* clearly indicate that "...compounds that have been shown to reduce Aβ peptide levels in transgenic mice are expected to reach the clinic soon." As such, claims 1-50 are directed to specific methods of use. The specification clearly provides evidence in accordance with the Declaration by Dr. Bi, and points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with the methods of use of the present invention. Thus, claims 1-50 have a specific, substantial and credible utility. Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

4. ***Rejections Under 35 U.S.C. § 112, First Paragraph***

Claims 1-50 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Each of the Examiner's concerns and, in turn, Applicants' responses to those concerns are set forth hereinbelow.

a. The Examiner has rejected claims 1-50, stating that the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above in connection with the § 101 rejection.

As explained above, the invention recited in claims 1-50 has a specific, substantial and credible utility. As such, the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

b. The Examiner has rejected claims 1-35, as allegedly containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Office Action, the claims read on modulating APP processing *in vitro*, modulating APP processing inhibition in mammals with below normal APP processing activity, modulating APP processing inhibition in mammals with normal APP processing activity, or in asymptomatic mammals with upregulated APP processing activity. The Office Action alleges that the specification fails to teach any benefit to be gained from such actions. Applicants respectfully traverse the rejection.

In response to the rejection, Applicants respectfully direct the Examiner's attention to the attached Declaration of Dr. Xiaoning Bi, pursuant to 37 C.F.R. § 1.132. In this Declaration, Dr. Bi sets forth the following:

> [t]he specification clearly describes the subject matter as to convey to one skilled in the relevant art that the inventors had possession of the claimed invention. The specification provides several Examples that teach *in vitro* and *in vivo* assays that assess the effects of test compounds on processing of APP and τ-protein. In my opinion, it would not require undue experimentation for one of skill in the art to obtain functional inhibitors of Formula I by following the protocols set forth in the Example section of the present specification. In my opinion, ***compounds that can modulate APP processing in vitro and modulate APP processing inhibition in mammals with below normal APP processing activity, or in asymptomatic mammals with upregulated APP processing activity, are useful in retarding the progression of neurological disorders.***

According to Dr. Bi, modulating APP processing *in vitro* and modulating APP processing in mammals with below normal APP processing activity, or in asymptomatic mammals with upregulated APP processing activity, are useful for retarding the progression of neurological disorders. Furthermore, Dr. Bi asserts that the specification clearly sets forth procedures which can be followed by one of skill to identify the aspartyl protease inhibitors of the present invention for use in the methods of

the present invention without undue experimentation. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

c. The Examiner has rejected claims 36-50, as allegedly nonenabled. In making this rejection, the Examiner has alleged that the scope of the phrase "neurodegenerative disorders" cannot be deemed enabled.

As explained above, independent claim 36 and dependent claims 37-50 are directed to a method for treating a neurodegenerative disorder the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor of Formula I. According to the Dr. Bi and as stated in the specification, neurodegenerative disorders that can be treated using the aspartyl protease inhibitors of the present invention include, for example, those neurodegenerative disorders characterized by the accumulation of amyloid plaques or τ-protein. It is well-known in the art that such plaques containing large amounts of Aβ. Clearly, therapeutic agents that can decrease the formation of Aβ, as do the aspartyl protease inhibitors of the present invention, can play a beneficial role in retarding the progression of these neurodegenerative disorders. Examples of such neurodegenerative diseases include, but are not limited to, the following: Alzheimer's disease, Parkinson's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia (*e.g.*, dementia pugilistica) and head trauma.

As explained above and is demonstrated in the specification, the aspartyl protease inhibitors of Formula I of the present invention can be used to modulate the processing of an APP and a τ-protein. Thus, the claimed invention has a specific, substantial and credible utility in that claims 36-50 are directed to a method of use, and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of us. As such, the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

5. Rejection of claims containing "substituted alkyl", "substituted aryl", and "substituted heteroaryl"

The Examiner has rejected claims containing the terms "substituted alkyl", "substituted aryl", and "substituted heteroaryl". According to the Office Action, the definition of these terms in the specification allegedly "do not allow the public to understand the metes and bounds of the claims." Applicants respectfully traverse the rejection.

The terms "substituted alkyl", "substituted aryl", and "substituted heteroaryl" are clearly defined in the specification on page 11, lines 9-15 and lines 25-32, and page 13, lines 13-22. In addition, several examples of substituted alkyls, substituted aryls, and substituted heteroaryls are set forth in the specification (*see*, page 11, lines 9-15 and lines 25-32, and page 13, lines 13-22 of the specification). Clearly, one of skill in the art can identify other substituted alkyls, substituted aryls, and substituted heteroaryls suitable for use in the present invention ***without*** undue experimentation. The claimed compound containing these substituted alkyls, substituted aryls, and substituted heteroaryls are aspartyl protease inhibitors of Formula I. The specification teaches one of skill in the art a number of procedures for testing the activity of such aspartyl protease inhibitors (*see*, page 31-36 of the specification). These assays include, for example, *in vitro* assays that assess the effects of test compounds on processing of APP, *in vivo* assays to evaluate the ability of compounds to modulate processing of APP, and assays to measure the ability of aspartyl protease inhibitors to modulate the processing of τ-protein.

Since 1) the terms "substituted alkyl", "substituted aryl", and "substituted heteroaryl" are terms of art that are routinely used by those of skill in the art; 2) such terms are defined in the specification as originally filed; 3) the claims are directed towards compounds that are aspartyl protease inhibitors of Formula I; and 4) the specification teaches a number of assays to test the activity of such compounds, the present invention clearly allows the public to understand the metes and bounds of the claims. In addition, Applicants would like to point out that the compounds recited in the method claims of the present application containing the terms "substituted alkyl",

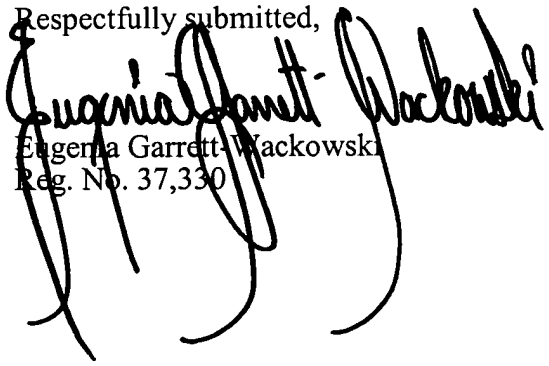
"substituted aryl", and "substituted heteroaryl" are claimed in above-mentioned U.S. Patent No. 6,150,416, issued November 21, 2000. Therefore, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Paragraph beginning at line 10 of page 1 has been amended as follows:

--This application is a continuation-in-part of 09/018,226, now U.S. Patent No. 6,150,416, issued November 21, 2000, and claims the benefit of that application, U.S. Provisional Application No. 60/125,958, filed March 24, 1999, and U.S. Provisional Application No. 60/036,903, filed February 4, 1997, the disclosures of which are incorporated by reference. This invention was made with Government support under Grant (Contract) Nos. RO1 GM53696 and RO1 GM50353 awarded by the National Institutes of Health. The Government has certain rights in this invention.--